CPC

Progressive symptoms and signs following institution of highly active antiretroviral therapy and subsequent antituberculosis therapy: immune reconstitution syndrome or infection?

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A 36 year old man presented with weight loss, cough, fever, and exertional dyspnoea shortly after a diagnosis of HIV infection. Symptoms and initial radiological abnormalities worsened after highly active antiretroviral therapy was started. An eventual diagnosis was established but multiple problems occurred throughout the treatment period. Differentiation between immune reconstitution inflammatory syndrome and an infective cause was problematic.

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CASE PRESENTATION
(Dr R F Miller)

A 36 year old white homosexual man was admitted to hospital in mid-November 2003. He gave a history of 7 kg weight loss over the preceding 3 months and a 3 week history of a minimally productive cough, mild exertional dyspnoea, and fever. Over the 4 days before admission his fever had worsened, he had become more short of breath on exertion, and experienced nausea and malaise. He was found to be HIV-1 antibody positive 1 month previously; at this time the CD4 count was 110 cells $\times 10^6$/l and HIV viral load was 1 421 900 copies/ml. Two weeks before admission the patient began co-trimoxazole 960 mg once a day, as primary prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP), and highly active antiretroviral therapy (HAART) consisting of Combivir (zidovudine and lamivudine) and efavirenz. At that time chest radiography was performed (fig 1) and sputum was ''smear negative'' for alcohol and acid fast bacilli (AAFB). His medical history was unremarkable and he had no family history. Before starting co-trimoxazole and HAART he was not taking any medication. He rarely drank alcohol and was a non-smoker.

IMAGING
(Dr P J Shaw)

There is parenchymal consolidation in the right apex extending inferiorly into the upper pole of the right hilum with early small volume right hilar lymphadenopathy.

CASE PRESENTATION
(Dr Miller)

On examination at the time of admission the patient was pyrexial at 37.9℃ and dyspnoeic at rest. He had oral hairy leucoplakia, oral candida, and a faint erythematous rash. There was no peripheral lymphadenopathy and examination of the cardiovascular, abdominal, and nervous systems was normal. Initial investigations showed normal urea and electrolytes and liver function tests. The C reactive protein (CRP) was 168 IU/l (normal <5 IU/l). A full blood count showed haemoglobin (Hb) to be 11.9 g/dl with a normal mean cell volume, and white blood cell count (WBC) of 6.4×10^9/l. Lactate dehydrogenase (LDH) was marginally elevated at 483 IU/l (normal 200–450 IU/l). A repeat chest radiograph was taken on admission (fig 2).

IMAGING
(Dr Shaw)

There is progression of the consolidation with an increase in right hilar lymphadenopathy and development of right paratracheal lymphadenopathy.

CASE PRESENTATION
(Dr Miller)

At this point, two sets of blood cultures looking for bacteria (including mycobacteria) and fungi were sterile. Three sputum samples were ''smear negative'' for AAFB. The rash was ascribed to co-trimoxazole and after stopping this drug the rash faded within 36 hours. Dapsone was substituted for co-trimoxazole as prophylaxis for PCP. What thoughts do you have about the presentation and what investigations should be prioritised?

DISCUSSION
(Panel: Dr M Shahmanesh, Dr M D Talbot, Dr M J Wiselka)

He was short of breath at rest and the chest radiographic abnormalities do not explain the severity of his symptoms. What were the resting

Abbreviations: AAFB, alcohol and acid fast bacilli; BAL, bronchoscopic alveolar lavage; BM, bone marrow; CRP, C reactive protein; HAART, highly active antiretroviral therapy; Hb, haemoglobin; IRIS, immune reconstitution inflammatory syndrome; LDH, lactate dehydrogenase; MDR-TB, multidrug resistant tuberculosis; PCP, *Pneumocystis jirovecii* pneumonia; WBC, white blood cell

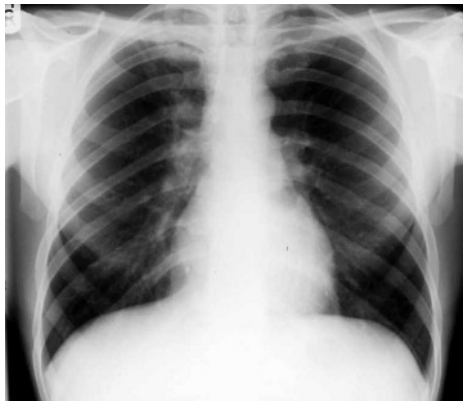

Figure 1 Chest radiograph, taken in October 2003, showing parenchymal consolidation in the right apex extending inferiorly in to the upper pole of the right hilum with early small volume right hilar lymphadenopathy.

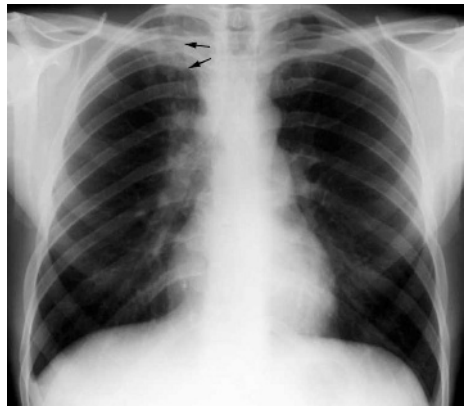

Figure 2 Chest radiograph, taken in mid-November 2003 on admission to hospital, showing progression of the consolidation with an increase in right hilar lymphadenopathy and the development of right

oxygen saturation levels and was bronchoscopy considered?

CASE PRESENTATION
(Dr Miller)

Resting oxygen saturation levels were normal and there was no desaturation, which mitigates against a diagnosis of PCP. At bronchoscopy analysis of bronchoscopic alveolar lavage (BAL) fluid was negative for *P jirovecii,* bacteria, and AAFB. On this basis PCP was thought unlikely. A computed tomography (CT) scan of the thorax was performed (fig 3).

IMAGING
(Dr Shaw)

Thoracic CT imaging showed consolidation lying in the apicoposterior segment of the right upper lobe, together with right paratracheal and anterior mediastinal lymphadenopathy.

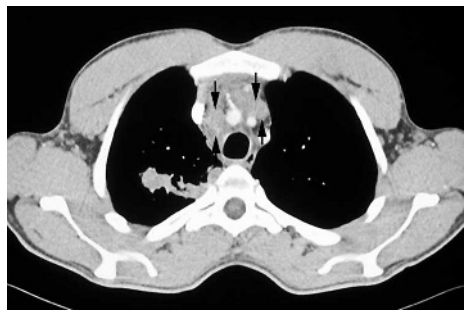

Figure 3 CT scan of thorax, performed in mid-November 2003, demonstrating that the consolidation lies in the apicoposterior segment of the right upper lobe together with right paratracheal and anterior mediastinal lymphadenopathy (arrows).

DISCUSSION
(Panel)

In a differential diagnosis one would definitely have to think of tuberculosis. It is possible that the patient has lymphoma with B symptoms, or Castleman disease and a coexisting lower respiratory tract infection; histoplasmosis may also enter the differential diagnosis depending on the travel history. Immune reconstitution inflammatory syndrome (IRIS) may be complicating the clinical picture.

CASE PRESENTATION
(Dr Miller)

The patient's symptoms persisted. Would you begin empirical treatment for tuberculosis?

DISCUSSION
(Dr Shahmanesh)

It would not be unreasonable to give antituberculosis treatment as there is a clear end point to look at—that is, the size of the mediastinal nodes.

CASE PRESENTATION
(Dr Miller)

We were nervous about starting antituberculosis therapy as it was not clear whether IRIS was already present or might have been exacerbated by starting therapy. Additionally drug-drug interactions and potential adverse drug effects, with the difficulties of ascribing a cause made us cautious. Would you consider any further investigations?

DISCUSSION
(Panel)

A mediastinoscopy to obtain tissue would be appropriate. How likely is IRIS and what would be the timing of it in relation to starting antiretroviral therapy?

CASE PRESENTATION
(Dr Miller)

For mycobacterial infection the median time for IRIS to occur is between 17 and 22 days, but may it occur up to 7 months, or later.[1 2]

DISCUSSION
(Panel)

The patient's symptoms started before HAART, so the presentation cannot be explained by IRIS alone, but the progression of symptoms accelerated after starting HAART. What about performing an interferon γ test, such as a QuantiFERON-TB or T.SPOT.TB test? There have been concerns that interferon γ tests may not provide useful information in patients with HIV induced immune suppression, but a recent study suggests that test performance is not impaired, even in patients with very low CD4 counts.[3]

An interferon γ test might provide useful information. If it was positive it would support the diagnosis of tuberculosis. However, management has changed; 2 years ago, at the time of this patient's presentation interferon γ tests were not available.

CASE PRESENTATION
(Dr Miller)

In the face of persistent symptoms and negative blood, urine, sputum, and BAL fluid cultures, the patient was referred for mediastinoscopy and lymph node biopsy 2 weeks after admission.

PATHOLOGY
(Dr C Bacon)

The mediastinal lymph node contained large areas of necrotic tissue surrounded by a predominantly lymphocytic inflammatory cell infiltrate with numerous macrophages (fig 4). In some areas the macrophages were clustered in ill formed granulomata. Several poorly developed multinucleate giant cells were present. Special staining revealed many AAFB. Grocott and periodic acid Schiff stains for fungi were negative.

CASE PRESENTATION
(Dr Miller)

At this point the original sputum sample from late October and the three consecutive samples sent in mid-November were reported to be growing AAFB. In early December 2003 the patient began antituberculosis therapy with rifampicin, isoniazid, and pyrazinamide. The dose of efavirenz was increased to 800 mg once a day because of the interaction with rifampicin.[4] Over the next 2 weeks he experienced worsening fever, sweats, and cough. At this stage *Mycobacterium tuberculosis* had been identified in the BAL specimen. The *RpoB* gene was mutated, suggesting resistance to rifampicin. Formal resistance testing was pending. In London 95% of all rifampicin resistant isolates of *M tuberculosis* are also isoniazid resistant, so if this finding was confirmed this would represent multidrug resistant tuberculosis (MDR-TB). What treatment changes are indicated?

DISCUSSION
(Dr Wiselka)

I would change treatment now and not wait. The *RpoB* gene test is 95% accurate. If he has MDR-TB he will need at least five active drugs including one parenterally administered; this may be difficult to achieve if the full sensitivities are not yet known.

CASE PRESENTATION
(Dr Miller)

In late December the patient stopped rifampicin and isoniazid and started ofloxacin, prothionamide, ethambutol, and streptomycin: pyrazinamide was continued. The dose of efavirenz was reduced to 600 mg 3 weeks after rifampicin was stopped. At this point the CD4 count was 230 cells $\times 10^6$/l and viral load 900 copies/ml. The patient had become anaemic. How should this be investigated?

DISCUSSION
(Panel)

The situation is very complex with many potential causes of anaemia. It might be worth doing a bone marrow (BM) aspirate and trephine; however, BM aspirate rarely yields a diagnosis, apart from mycobacterial infection—which is usually identified by culture—and trephine has a low diagnostic yield.[5] In patients with cytopenia and fever BM examination has a higher yield.

PATHOLOGY
(Dr Bacon)

The BM aspirate showed a dysplastic hypercellular marrow with granulomata. The trephine showed normocellular trilineage maturing haematopoiesis with reactive granulocytic hyperplasia and an increase in eosinophils and their precursors. The erythroid precursors and megakaryocytes showed mild dysplastic features. Occasional well defined granulomata were present and there were several polymorphic reactive lymphoid aggregates (fig 5). A Ziehl-Neelsen stain for AAFB was negative.

CASE PRESENTATION
(Dr Miller)

Culture and speciation are mandatory as a granulomatous response may occur with atypical mycobacteria in the context of IRIS.[6] Culture of the BM aspirate was negative. At this stage zidovudine was changed to tenofovir in view of his anaemia. Thus, in January 2004, the antiretroviral regimen consisted of tenofovir, lamivudine, and efavirenz. Would the panel like to comment on the efficacy of this regimen?

DISCUSSION
(Dr Shahmanesh)

This is a very effective combination against HIV, with few side effects. This regimen is equally efficient in reducing viral load compared to his previous regimen. It does, however, present the patient with three drugs all with a low resistance threshold. In a non-adherent patient this might severely limit future treatment options.

CASE PRESENTATION
(Dr Miller)

In late January 2004, antimycobacterial sensitivities became available. All isolates of *M tuberculosis* were resistant to

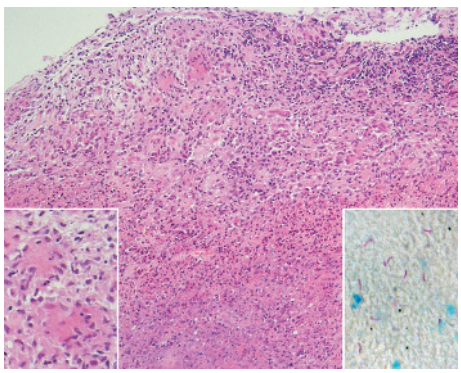

Figure 4 Biopsy of the mediastinal mass showing necrotic tissue (lower half of field) surrounded by poorly developed granulomatous inflammation (upper half of field and left inset). A Ziehl-Neelsen stain showed numerous acid fast bacilli (right inset).

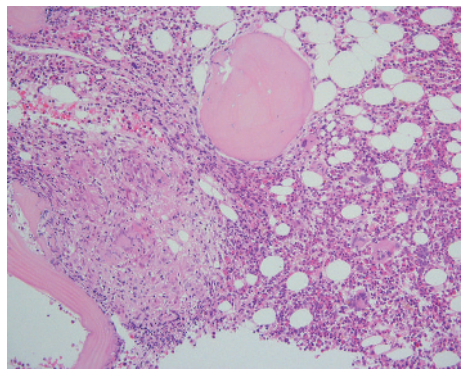

Figure 5 Bone marrow trephine biopsy showing normocellular trilineage maturing haematopoiesis with reactive and dysplastic features. Occasional granulomata were present.

fluoroquinolones and prothionamide, but sensitive to pyrazinamide, ethambutol, cycloserine, and macrolides. Thus, the patient had received only three effective drugs. Given that at least two drugs should be changed in order to prevent sequential resistance, how would you modify the treatment regimen?

DISCUSSION
(Panel)
Start two new drugs, including a macrolide.

CASE PRESENTATION
(Dr Miller)
The patient stopped ofloxacin and prothionamide. Cycloserine and clarithromycin were started and streptomycin, ethambutol, and pyrazinamide were continued. By now, the patient had developed a severe reactive depression as a result of the diagnosis of HIV and of MDR-TB. Do you have any worries regarding treatment?

DISCUSSION
(Dr Wiselka, Dr Shahmanesh)
Cycloserine has psychiatric side effects and efavirenz may also cause psycho-morbidity.

CASE PRESENTATION
(Dr Miller)
Efavirenz related psychiatric problems usually occur within the first few weeks of starting therapy. Cycloserine is associated with an increased risk of suicide, even in individuals without a background of depression. The patient was initially monitored in hospital. By mid-February 2004 the CD4 count was 200 cells $\times 10^6$/l and viral load 80 copies/ml. This is 3–4 months after the initial presentation, the patient having received a relatively suboptimal regimen of antituberculosis therapy. Further sputum samples were obtained and a chest radiograph was performed (fig 6).

IMAGING
(Dr Shaw)
The chest radiograph showed more extensive dense consolidation in the right apex with diffuse infiltration of the right upper lobe associated with early volume loss. The extensive right paratracheal lymphadenopathy has progressed.

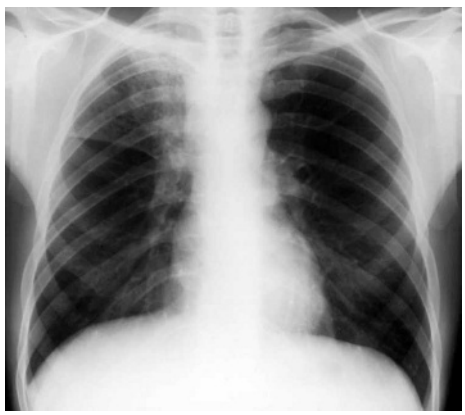

Figure 6 Chest radiograph, taken mid-February 2004, showing more extensive dense consolidation in the right apex with diffuse infiltration of the right upper lobe associated with early volume loss. The extensive right paratracheal lymphadenopathy has progressed.

CASE PRESENTATION
(Dr Miller)
It took 17–18 days to culture mycobacteria from the first specimens obtained in November. The current specimens were ''smear'' negative and culture was initially negative, but *M tuberculosis* grew after 5 weeks. Thus, viable organisms persisted over 3 months after starting treatment.

With respect to the clinical course, the patient then developed a rash, which was ascribed to tenofovir. Tenofovir was stopped and didanosine substituted. The rash persisted for 6–7 days and then resolved. In early March 2004 the patient reported an increase in size of a lymph node on the right side of his neck. Of note, adherence was good as directly observed therapy was being used. The CRP was 150–250 IU/l and LDH 600–700 IU/l. Clearly, something was activating lymphocytes. A thoracic, abdominal, and pelvic CT scan was done (fig 7).

IMAGING
(Dr Shaw)
In the chest there is extensive consolidation with air bronchograms in the right upper lobe which is contiguous with necrotic enlarged right paratracheal and a single anterior mediastinal lymph node. Rim enhancement of the nodes is seen. This is typical of infection, but may also be seen with IRIS.[1] The pelvic and abdominal images are normal.

DISCUSSION
(Dr Shahmanesh, Dr Wiselka)
It appears that the primary disease is progressing. This appears to be an extension of the tuberculosis, but it is likely that 10% of the problem is tuberculosis and 90% is IRIS.

CASE PRESENTATION
(Dr Miller)
The enlarging lymph nodes in the mediastinum and the neck were worrying. Our differential diagnosis included tuberculosis with IRIS, or another process, such as lymphoma. The elevated LDH, arising from activated lymphocytes, could have been caused by a lymphoproliferative disorder, such as lymphoma or Castleman disease, or to IRIS.

IMAGING
(Dr Shaw)
A chest radiograph in mid-April 2004 showed progression of the paratracheal lymphadenopathy, which is inseparable from the consolidation in the right upper lobe medially. There is persistent volume loss (fig 8).

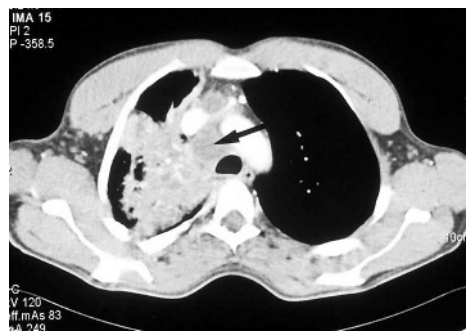

Figure 7 CT scan of thorax, performed at the end of March 2004, showing extensive consolidation with air bronchograms in the right upper lobe which is contiguous with necrotic enlarged right paratracheal lymph nodes. Rim enhancement of nodes is seen.

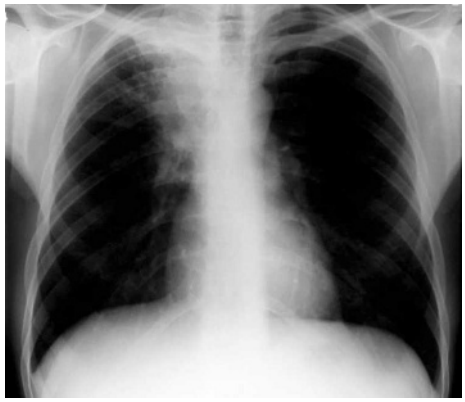

Figure 8 Chest radiograph, taken in mid-April 2004, showing progression of the right paratracheal lymphadenopathy, which medially is inseparable from the right upper lobe consolidation.

CASE REPORT
(Dr Miller)

At this point streptomycin was stopped, as the maximum dose had been reached. Cycloserine, ethambutol, pyrazinamide, and clarithromycin were continued. He had a CD4 cell count of 200 $\times 10^6$/l and viral load of <50 copies/ml. By late April the right cervical node had increased in size to 4×5 cm. What investigation is indicated?

DISCUSSION
(Dr Wiselka)

I would attempt aspiration of the node. If pus was obtained, I would get a stain done for AAFB and also culture it for mycobacteria. If aspiration was unsuccessful, I would ask for a surgical excision biopsy. Surgical intervention may result in chronic sinus formation, but tissue rather than cells is needed to diagnose lymphoma.

CASE PRESENTATION
(Dr Miller)

We obtained an ultrasound guided fine needle aspirate of the node. Histology showed inflammatory necrosis, with lymphocytes, polymorphs, and AAFB. Culture of the aspirate was negative, so the AAFB are dead. We were left with the dilemma—was this IRIS or tuberculosis, or both? We thought this was IRIS. Following aspiration the lymph node underwent slow involution. By late August 2004 he had a CD4 count of 380 cells $\times 10^6$/l and a viral load of 80 copies/ml. A further chest radiograph was done.

IMAGING
(Dr Shaw)

The chest radiograph showed that there has been marked improvement in the paratracheal lymphadenopathy. There was persistent consolidation (fig 9).

CASE PRESENTATION
(Dr Miller)

In the autumn of 2004 the neck lymphadenopathy had completely resolved and dapsone was stopped as the CD4 count had been more than 250 cells $\times 10^6$/l for more than 3 months. The patient started training for extreme sports but developed disproportionate myalgia for several days after each episode of exercise. How would you investigate this?

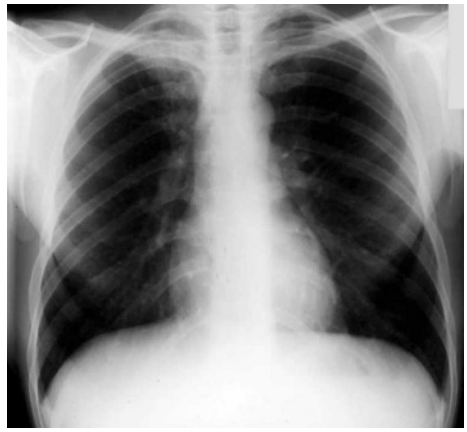

Figure 9 Chest radiograph, taken in late August 2004, showing marked reduction in size of the paratracheal lymphadenopathy. There is persistent consolidation.

DISCUSSION
(Dr Shahmanesh)

Do any drugs cause a myositis? Was creatine kinase measured? Is this mitochondrial toxicity from didanosine?

CASE PRESENTATION
(Dr Miller)

Creatine kinase, aspartate aminotransferase and LDH were normal. A resting uncuffed venous lactate level was 1.32 mmol/l (normal 0.4–2.2 mmol/l). A post-exercise venous lactate level was 6.7 mmol/l: this result should have been normal, as the ability of the liver to clear lactate is huge. What investigation would you do next?

DISCUSSION
(Panel)

A muscle biopsy is indicated.

CASE PRESENTATION
(Dr Miller)

The patient declined a muscle biopsy as he wished to pursue his sporting activities. It was thought that mitochondrial toxicity was most likely, and that didanosine was the likely culprit. Didanosine was stopped and tenofovir was restarted. The patient's symptoms resolved and he was able to compete in his extreme sporting activity.

By March 2005 the CD4 cell count was 450 cells $\times 10^6$/l, the viral load was undetectable and a chest radiograph was normal. In May 2005, the patient developed joint pain, starting in his right knee and then in the right hallux. He also had intermittent explosive diarrhoea, and aggressive warts developed on his hands and lips.

Does the panel have any thoughts?

DISCUSSION
(Panel)

What was his uric acid level? Pyrazinamide may cause hyperuricaemia.

CASE PRESENTATION
(Dr Miller)

The serum urate was 680 μmol/l (normal <420 μmol/l) and renal function was normal. The joint problems were thought to be caused by pyrazinamide, which was stopped and he continued to take cycloserine, clarithromycin, and ethambutol. A repeat serum urate level was normal. Stool cultures were negative, but the diarrhoea stopped on discontinuing

Key points

- Immune reconstitution inflammatory syndrome (IRIS) to mycobacteria may occur within the first few weeks of starting HAART
- Paradoxical lymph node enlargement during treatment of HIV and tuberculosis may be caused by progressive tuberculosis, IRIS, or a combination of both. Other causes, such as lymphoma need to be considered
- Mutations in the *RpoB* gene infer rifampicin resistance; this finding should be confirmed by formal resistance testing
- Clinicians should be alert to the possibility of MDR-TB. Identification of MDR-TB has important implications for treatment and infection control

pyrazinamide: it is unusual for diarrhoea to be caused by pyrazinamide after many months of exposure. This was not thought to be infective diarrhoea or an enteric arthropathy because of the negative stool cultures and the temporal relation between symptom resolution and stopping pyrazinamide. The warts were thought to be another manifestation of IRIS. By late June 2005 the CD4 count was 400 $\times 10^6$/l and viral load $<$50 copies/ml. The patient will continue cycloserine, clarithromycin, and ethambutol indefinitely

ACKNOWLEDGEMENTS

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Conflict of interest: Dr R F Miller is co-editor of, and Dr M Shahmanesh is journal ombudsman for, *Sexually Transmitted Infections*, part of the BMJ Publishing Group.

REFERENCES

1 **Buckingham SJ**, Haddow LJ, Shaw PJ, *et al*. Immune reconstitution inflammatory syndrome in HIV-infected patients with mycobacterial infections starting highly active anti-retroviral therapy. *Clin Radiol* 2004;**59**:505–13.
2 **Lawn SD**, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect Dis* 2005;**5**:361–73.
3 **Dheda K**, Lalvani A, Miller RF, *et al*. Performance of a T-cell-based diagnostic test for tuberculosis infection in HIV-infected individuals is independent of CD4 cell count. *AIDS* 2005;**19**:2038–41.
4 **Pozniak AL**, Miller RF, Lipman MC, *et al*. BHIVA treatment guidelines for tuberculosis(TB)/HIV infection 2005. *HIV Med* 2005;**6**(Suppl 2):62–83.
5 **Llewelyn MJ**, Noursadeghi M, Dogan A, *et al*. Diagnostic utility of bone marrow sampling in HIV-infected patients since the advent of highly active antiretroviral therapy. *Int J STD AIDS* 2005;**16**:686–9.
6 **Whitely W**, Tariq A, Peters B, *et al*. Pyrexia of undetermined origin in the era of HAART. *Sex Transm Infect* 2000;**76**:484–8.